Allele predicted accelerated rate of cognitive decline in Alzheimer's disease

Question

In patients newly diagnosed with Alzheimer's disease, what effect do different apolipoprotein E (Apo E) genotypes have on the rate of cognitive decline?

Design

Inception cohort followed 1–6 years ($\bar{x}$ 2.47 years)

Setting

Health maintenance organization in Seattle, WA

Participants

A total of 201 patients were included. They had all been diagnosed with Alzheimer's disease within the previous year, based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised, and the National Institute of Neurological and Cognitive Disorders and Stroke-Alzheimer's Disease and Related Disorders Association. Patients with other central nervous system conditions or major psychiatric disorders were excluded.

Assessment of prognostic factors

Patients were grouped according to their Apo E genotype: ε2/3 (n=14), ε3/3 (n=75), ε3/4 (n=82), and ε4/4 (n=30).

Main outcome measure

Annual rate of cognitive decline assessed by total scores on the Dementia Rating Scale (DRS) derived from 5 subscales: attention, memory, initiation and perseveration, conceptualization, and construction.

Main results

All patients had baseline and ≥1 DRS total score. At the mean DRS score of 105 for this patient sample, the ε4/4 group had a greater rate of decline than the ε2/3 group (P<0.003). The differences in rate of decline were less pronounced compared with the ε3/3 group (P<0.076) and the ε3/4 group (P<0.055). At a DRS score of 80, the rate of decline in the ε4/4 group was greater than in the ε2/3 group (P<0.001) and the ε3/4 group (P<0.021), with a smaller difference compared with the ε3/3 group (P<0.174) (see Table 1). At both cut-off points, the rate of decline was slower in the ε2/3 group than in the ε3/3 and ε3/4 groups. In addition, older age predicted a slower rate of decline (P<0.001).

Conclusions

Patients newly diagnosed with Alzheimer's disease who were homozygous for the apolipoprotein E ε4 allele had an increased rate of cognitive decline compared with other genotypes. Patients with the ε2/3 allele had a slower rate of decline.

Table 1 *Rate of decline compared with Dementia Rating Scale score*

Score on Dementia Rating Scale	Rate of decline (points/year)			
	ε2/3	ε3/3	ε3/4	ε4/4
105	5.8	9.3	9.6	11.9
80	9.7	18.2	15.8	22.2

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Neurology 1998;51:149-53.

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COMMENTARY

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The search for biological markers to confirm the clinical diagnosis of Alzheimer's disease (AD) has been prompted by the assumption that new treatments are most likely to slow or halt disease progression rather than reverse existing damage. Human Apo E, previously known for its role in cholesterol transport and plasma lipoprotein metabolism, has emerged as a major genetic risk factor for AD.

The Apo E ε4 allele has been shown to confer an increased risk of AD, occurring in up to 50% of cases.[1] From a clinicopathological viewpoint, the Apo E ε4 allele appears to lower the age of onset of AD and increase the amount of A β deposition in the brain.[2] Few studies support the implications of genotype differences in disease severity or rate of decline.[3,4] In that context, this study contributes to knowledge about the molecular genetics of AD.

The study includes the largest inception cohort of patients with AD in whom longitudinal data and Apo E status have been reported. Another strength of the study is the use of the DRS's broad range of scores to measure decline and avoid the floor effects of other instruments (for example, the Mini Mental State Examination). Furthermore, the study was able to examine the effects of Apo E genotype status on disease progression. Statistically significant differences were detected in the rate of decline between the ε4/4 group (fastest) and the ε2/3 group (slowest), while similar (intermediate) rates were detected for the ε3/4 and ε3/3 groups. Finally, the results were robust to the manipulation of age at onset as a covariate or as a correlate of rate of decline.

The study provides further evidence for the hypothesis that Apo E plays a mechanistic part in the neuropathological progression of Alzheimer's disease as well as in its onset. The findings support the previously established clinical utility of Apo E testing[5] and suggest its possible role as a prognostic indicator in some patients presenting with dementia.

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